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Leading article: Research with children and young people – not on them

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Research *with* children and young people – not *on* them

"It is not ethical to conduct research on children." This comment is typical of objections in the past to studies with children. The continuing legacy of this viewpoint is that today's evidence base for the care provided to children is not as strong as it could be. Thankfully, however, this is now changing. We have learnt that, rather than protecting children and young people *from* research, we need to protect them *through* research and there is now a strong recognition of the need for ethically and scientifically robust ways to conduct relevant clinical research with children. [1] The recent Nuffield Council on Bioethics report *Children and clinical research: ethical issues* is helping the continued evolution of this thinking. [2] This article summarises some of its main findings and recommendations.

The report examined the question: how can we ethically undertake the research needed to ensure their healthcare services are safe and effective, given that research often involves burdens and risks? Moreover, what role should children, young people and parents themselves play in influencing how research studies are carried out, and how can their voices help influence the wider research agenda? There were 19 key recommendations (Summary- <http://nuffieldbioethics.org/wp-content/uploads/Children-and-clinical-research-key-recommendations.pdf>). The Nuffield Council on Bioethics explored these issues through an expert Working Party, supported by a stakeholder group involving young people and parents. Throughout the project, input was sought widely from young people, parents and professionals concerned with clinical research, in the UK and beyond. Views and experiences were sought through web-based surveys, an open 'call for evidence' and face-to-face meetings; through school projects in the UK and Kenya; and through networks of research professionals. While the focus of the report, and its concrete recommendations, are targeted primarily on the UK, they sought to ensure that the ethical analysis and conceptual recommendations had as wide a resonance as possible.

Clinical Research and its context

In determining the scope of the report, what constitutes 'clinical research' was considered as any form of research encounter with children and young people that holds out the prospect of improving healthcare, including preventative healthcare, in the future. Therefore clinical research covers a wide range of potential activities, with widely differing potential burdens and benefits for participants and their families. The context in which the research takes place can create different ethical challenges. To just think about 'children' as a homogenous group, as the law and some research regulation can do, is not always helpful. From newborn babies through to young people on

the verge of adulthood, they will have vastly different experiences, capacities and roles with respect to decision making. Families themselves can also be very different, including in their size, form, parenting style, health status, social and economic situation, educational opportunities, and intellectual capacities.

Some examples of this are: a 3 year old whose parents wish her to take part in a vaccine trial; a 7 year old with cancer whose treatment potentially includes research elements; a 10 year old with asthma taking part in research about his experiences of healthcare; a 14 year old taking part in research about health-related behaviours, that she might not wish her parents to know about. The report highlights that it is not just about age, the child's state of health, parenting style & child's consequent experience of independent decision-making, family attitudes to professionals and healthcare, to name but a few, will all influence how these children & families respond to an invitation to take part in research. All of these factors need to be considered from the beginning when planning a research study, then writing a protocol, recruiting to a study and through to the presentation of that research to the potential participants.

What is ethically different about children?

The Nuffield report identified two important features which are significant in developing an ethical approach to research with children: the developmental nature of childhood, from complete dependence at birth to the growing independence of young adulthood; and the role of parents and wider family in nurturing, sustaining and shaping that development. The report usefully created three paradigm cases or scenarios, in which a child's or young person's potential for input into a decision about research, and the corresponding role of their parents, raises distinct ethical questions (figure 1). All children at the beginning of their lives will fall into Case one, and most (although not all) will progress over time through Case two to Case three. This progression is not simply linear, however, and will also be dependent on the nature of the research decisions against the background of the emotional, physical and mental health of the child or young person at the time. It is important to ask which case is applicable for *this* child and young person for *this* decision. For example a 12 year old may be in Case 2 for some decisions and Case 3 for others, while a very ill 16 year old might be in Case 2 or even Case 1, when they would usually be in Case 3. These Cases overall are helpful in giving researchers a framework in which to consider their protocols, and even more importantly the potential impact of study design on particular participants, and their communication strategies with children and families.

The Vulnerability of Children.

Another reason for the historical caution with regards to paediatric research is that much of the regulation of clinical research involving children, from international ethical declarations to national law, presents children as inherently vulnerable. [3] This was strongly challenged during the development of the Nuffield report, particularly by children and young people themselves. It was highlighted that an unthinking response to perceived or actual vulnerability may exclude children from opportunities to participate, and prevent valuable research taking place. Instead of treating concerns about potential vulnerability as an automatic brake on research, a better response would be to treat such concerns as an *alert*, and to ask the question: "Does this research raise particular ethical challenges for children and young people, and if so, what can I do about them?" By working in partnership with children, young people and families throughout the whole research endeavour, the risks that children might be placed in situations that make them vulnerable can be minimised.

Challenges can best be explored in light of children's and young people's own perceptions of the demands of the study. Genuine partnership will help to ensure that important aspects of the research question have been considered from the perspective of those whom the research aims to benefit and who are in a similar situation to potential participants. Their input on factors such as missing school, repeated blood tests and the quality/accessibility of patient information is invaluable and means that researchers are aware of those aspects of study design that might be of concern to prospective participants, so that wherever possible, these concerns can be ameliorated. The young people attending stakeholder events during the creation of the report identified ways by which they might feel better supported and thereby less prone to vulnerability: being prepared, parental support and feeling listened to were all cited. Hence the information we make available during a research study is a crucially important factor to arm children and their families against vulnerability – both in terms of how we communicate about the study itself, and how we work with children and families to support their decision-making. For this reason an important part of the Nuffield project included the creation of an animation to convey to even very young children what participation in a well-designed research study should be like (nuffieldbioethics.org/children).

Research Priorities for children and young people.

The Nuffield Report goes on to argue to move away from researching 'on' children it is important to genuinely involve them (and their families) from the outset, starting with the issue of setting

research priorities. A survey by the James Lind alliance (JLA) in 2008 showed that most research funders at the time “operated in a responsive mode”, relying on researchers to submit ideas. The JLA themselves have led the way in developing ‘priority-setting partnership’ involving patients, carers and clinicians together to identify priorities for research. This approach has led to inclusive partnerships exploring research priorities for improving the care of preterm babies [4] and teenagers with cancer.[5] This has been achieved with what would traditionally be considered very vulnerable populations.

Partnership and review of research

Further change will only occur if it is accompanied by a significant shift in attitude of those involved in paediatric medicine and research. Many studies struggle to recruit sufficient participants –which has sometimes been assumed to reflect patients’ reluctance towards research.[6] However, there is evidence that it is clinicians, rather than patients, who are the ones who are reluctant.[7] One study, for example, found that some clinicians were uncomfortable discussing research with families, and many tended to worry that they were burdening children and families just by inviting them to consider taking part in a study. But far from seeing research invitations as a burden or imposition, families have been found to be enthusiastic about taking part in research and wanted their clinicians to tell them if there was a suitable study available.[8,9]

To meet the concern of clinicians and parents and thereby avert undue hesitancy in inviting participation the Nuffield report developed the idea that an invitation to participate in research should constitute a “fair offer” to children and their families. This was seen to start with the fundamental role of the ethics committee (REC) and their review of the value of the research and its likely risks, benefits and burdens. The RECs role should be one of assurance for the public. They should not only confirm that the quality of the information given to parents, children and young people is good but also make a judgement on the reasonableness of the 'offer' presented. This role requires the continued participation of experts in relevant clinical fields within our RECs, and time needs to be given for experts to fulfil these roles. This need to be recognised as a core NHS duty and this will be a challenge in the current financial climate. A pool of additional experts willing to advise NRES RECs on an ad hoc basis could be further created to help with this, especially where the subject of the study falls outside the specialist expertise of REC members.

RECs should also routinely expect researchers to have involved children, young people and their parents in the design of their studies as they will be well placed to comment on the many practical features of research involvement, such as the number of visits, procedures planned (such as blood tests) and timings around the child's school day and social interactions. At a basic level their input on the comprehensibility of the study information is crucial. However, families are also well placed to advise on how to minimise the burdens of research for participants, and how to explain any risks clearly and concisely. Researchers who have not obtained this input should now be asked to justify why this has not been possible or appropriate and demonstrate how they have informed their research design in other ways. Groups such as the Young Persons' Advisory Groups (YPAGs) that have developed alongside the NIHR's Clinical Research Network: Children can play a key role in helping in this process and are an invaluable resource that should be supported in the long term.

Consent and Assent

Throughout the Nuffield report the issue of partnership is key, and it is seen as particularly crucial at the point when researchers approach children and their families with an invitation to consider taking part in a particular study. Wherever possible, researchers should seek to encourage shared decision-making: both with respect to the process and design of research, and to the decision about research participation itself. Young people in Case 3 have sufficient understanding and maturity to make their own decisions about participation, but will generally still rely on, and value parental support. Parents likewise still have a responsibility with respect to the welfare of their 'competent' child while they are still minors. Ethically, consent should thus be sought from both young person and their parent(s), even if in law parental consent is sufficient to authorise participation. Where the nature of the research is such that parental involvement is believed to be inappropriate, or might undermine the research objective or even threaten a young person's well-being, it may be ethically acceptable to approach children and young people in Case Three without parental knowledge or involvement. However, such approaches should be subject to specific review by a REC.

Where children and young people are in Case 2, they are not able to make their own decisions but *will* want to have a 'say' (in many cases a very strong say) in what affects them so directly. The Nuffield report suggests that the much contested requirement, in international and national guidance [10], that children should 'assent' to research, should be understood as requiring researchers to *involve* each child in Case 2 in the decision about research participation, as much as each child wants, and is able, to do. It is not a legal requirement in European and UK law but is

quoted in most of the international and national guidance frameworks (NRES guidance- <http://www.hra-decisiontools.org.uk/consent/principles-children.html>). How that process is subsequently documented (whether in an 'assent' form or in a range of other ways) is much less important than the child's own feeling that they have had a stake in the decision, and have been treated as an individual who matters.

In conclusion

Bringing these various threads together it is possible to be sympathetic to those who have worried about researching *on* children, whilst at the same time believing that there is an ethical imperative to push forward high quality ethically robust research *with* children and their families. Clinicians, researchers and ethics committees can work with children and young people to minimise the burdens of research, whilst at the same time maximising the sense of engagement and involvement in the process. By carefully crafting a 'fair offer' and empowering children and their families to consider that offer as it relates to their own circumstances can help move on from a narrative of vulnerability towards one of partnership. In turn, children and young people should no longer be left vulnerable to the host of harms associated with under-researched therapies and over-precautionary attitudes to research involvement. Since the report's publication in 2015 it has been taken forward enthusiastically by RCPCH, the NIHR's CRN Children & their 'GenerationR' young people's groups. The practical resources created by the project are freely available, including an animation in English and Spanish explaining research participation- Health research making the right decision for me. [2] It is hoped that by stimulating debate surround these issues, research *with* children and young people can move forward.

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Image legend

Figure 1: Paradigm cases for roles of child and parental input into the decision to take part in research.

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